Note: This document was archived on June 21, 2005 from the GHTF website.

Justification: The referenced documents are no longer the most current information available - See ISO TIR 14969:2004 in which GHTF SG#3 participated in drafting and incorporating the most current guidance.

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FINAL DOCUMENT

Title: Guidance On Quality Systems For The Design And Manufacture Of Medical Devices

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The document herein was produced by the Global Harmonization Task Force, a voluntary group of representatives from medical device regulatory agencies and the regulated industry. The document is intended to provide *non-binding* guidance to regulatory authorities for use in the regulation of medical devices, and has been subject to consultation throughout its development.

EXHIBIT

"II"

GUIDANCE ON QUALITY SYSTEMS FOR THE DESIGN AND MANUFACTURE OF MEDICAL DEVICES

Issue N^{o} 7
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0. Introduction

Regulatory control of medical device design and manufacture is developing in various ways in different countries or blocs. One approach which is gaining wide acceptance is that of quality systems which incorporate all the principles formerly known as Good Manufacturing Practice (GMP). A consensus is growing that a suitable quality system should incorporate the principles of ISO 9001 plus additional healthcare-related requirements specific to medical devices.

These additional health-care related requirements are embodied in the European standard EN 46001 and in the draft GMP Regulations of the USA, Japan and Canada.

This document provides guidance on the implementation of quality systems for medical devices, based on ISO 9001 (1994 version) and is organised according to the clause numbering of ISO 9001. For use in particular countries/blocs which may have GMP regulations of their own, the format and paragraph numbering may be changed but the content should remain the same. A non-exhaustive list of standards supportive of this guidance document is included as an Appendix.

It has been prepared by a group of representatives of industry and regulatory authorities from the Canada, EC, Japan and USA. It is regarded as acceptable guidance on the quality system requirements for medical devices in these countries.

The relationship of this document to other published guidance, and to the standards themselves, is illustrated in the following diagram.

		INTERNATIONAL	***CANADA***	***EC***	***JAPAN***	***USA***
Requirements	General	ISO 9001 ISO 9002 ISO 9003	CAN/CSA Q9001-91 Q9002-91 Q9003-91	EN 29001 EN 29002 EN 29003	JIS Z 9901 JIS Z 9902 JIS Z 9903	ANSI/ASQ C Q91 ANSI/ASQ C Q92 ANSI/ASQ C Q93
	Medical Device	ISO/DIS 13485 ISO/DIS 13488	Future adoption of ISO 9001	EN 46001 EN 46002	MHW GMP	FDA GMP
Guidance	General	ISO 9004-1 ISO 9000-2	CAN/CSA Q9004-92 Q9004.2-92	EN 29004	JIS Z 9904	
	Medical Device			EN 724 prEN 928 prEN 61272	JFMDA Guidance	Application Guidelines
		GUIDANCE ON QUALITY SYSTEMS FOR THE DESIGN AND MANUFACTURE OF MEDICAL DEVICES				

The text is based on ISO 9000-2 (1993) and extracts from EN 724, prEN 928 and prEN 61272. It should be read in conjunction with ISO 9004-1.

1. Scope

This document provides general guidance on the implementation of quality systems for medical devices based on ISO 9001. Such quality systems include those of the EU Medical Device Directives and the GMP requirements currently in preparation in Canada, Japan and USA. [It may be used for systems based on ISO 9002 by the omission of sub-clause 4.4].

The guidance given in this document is applicable to the design, development, production, installation and servicing of medical devices of all kinds. [Specific additional guidance referring to particular categories of medical device is given in Appendices.]

This document describes concepts and methods to be considered by medical device manufacturers who are establishing and maintaining quality systems. It is not intended to be directly used for assessment of quality systems.

This document describes examples of ways in which the quality system requirements can be met, and it is recognised that there may be alternative ways that are better suited to a particular device/manufacturer.

2. References

ISO/DIS 9001.2:1994: Quality Systems - Model for Quality Assurance in Design/Development, Production, Installation and Servicing.

ISO 9004-1:1994: Quality management and quality system elements - Part 1: Guidelines.

ISO 8402:1993: Quality vocabulary.

EN 46001:1993: Quality Systems - Medical Devices - Particular Requirements for the Application of EN 29001.

ISO 9000-2:1993: Generic guidelines for the application of ISO 9001, ISO 9002 and ISO 9003.

EN 724:1993: Guidance on the application of EN 29001/EN 46001 and EN 29002/ EN 46002 for non-active medical devices.

prEN 928:1991: Guidance on the application of EN 29001/EN 46001 and EN 29002/EN 46002 for the in-vitro diagnostics industry.

prEN 61272:1993: Guidance on the application of ISO 9001/EN 46001 and ISO 9002/EN 46002 for the active medical device industry.

3. Definitions

For the purposes of this document the definitions given in ISO 8402:1993 apply, together with those given below.

3.1 Advisory notice

A notice issued to provide information and/or advice on what action should be taken in the use, modification, disposal or return of a medical device.

3.2 Complaint

Any allegation, reported in any form to the supplier, of deficiencies related to the identity, quality, durability, reliability, safety or performance of a medical device.

3.3 Contract

Any legally binding agreement between the supplier and the purchaser concerning the supply of product or service. Note: a contract may be in writing, verbal or a combination of both.

3.4 Design

(Verb) To generate information from which a required product can become a reality.

(Noun) The set of instructions (eg specifications, drawings and schedules) necessary to construct a product.

3.5 Label

All written, printed or graphic matter:

a) on a medical device or any of its containers or wrappers; or
b) accompanying a medical device;

relating to identification, technical description or use of the medical device ut excluding shipping documents.

3.6 Labelling

The process of combining labels with medical devices

3.7 Product

The result of activities or processes.
Products may be subdivided into four generic product categories:

Generic Product Category	Kinds of Product
Hardware	Products consisting of manufactured pieces and parts, or assemblies thereof.
Software	Products, such as computer software, consisting of written, or otherwise recordable information, concepts, transactions or procedures.
Processed Materials	Products (final or intermediate) consisting of solids, liquids, gases or combinations thereof, including particulate materials, ingots, filaments or sheet structures. Note: Processed materials typically are delivered (packaged) in containers such as drums, bags, tanks, cans, pipelines, or rolls.
Services	Intangible products which may be the entire or principal offering, or incorporated features of the offering, relating to activities such as planning, selling, directing, delivering, improving, evaluating, training, operating or servicing for a tangible product.

Note: All generic product categories provide value to the customer only at the times and places the customer interfaces with, and perceives benefits from, the product. However, the value from a service often is provided primarily by activities at a particular time and place of interface with the customer.

3.8 Recall

When there is a risk of death or serious deterioration of the state of health:

- the return of a medical device to the supplier;
- its modification by the supplier at the site of installation;
- its exchange; or
- its destruction;

in accordance with the instructions contained in an advisory notice.

Recall may be occasioned by failure to comply with regulatory requirements.

3.9 Refurbishing

The processing or reprocessing to specified requirements of a medical device which has been previously released.

Note: Refurbishing applies also to repackaging and/or resterilization of medical devices, for example when a container that maintains sterility has been opened or damaged.

4. Quality system requirements

4.1 Management responsibility

4.1.1 Quality policy

When defining and documenting its quality policy, quality objectives and commitment to quality, supplier management should consider the following points:

The quality policy should be expressed in language which is easy to understand.
The quality policy should be relevant to the organisation, its other policies, the products or services provided, and the organisation's personnel.
The objectives should be achievable.

Management should demonstrate commitment visibly and actively on a continuing basis. Commitment can be demonstrated by activities such as the following:

- ensuring the organisation's personnel understand and implement the quality policy;

- initiating, managing, and following up on the implementation of the quality policy, including implementation of the quality system;

- not accepting deviations from quality policy or wasted resources in any part or aspect of the organisation.

- providing adequate resources and training to support quality system development and implementation.

See also 4.1, 4.2, 4.3, 5.2.1 and 5.3.1 of ISO 9004-1.

4.1.2 Organisation

4.1.2.1 Responsibility and authority

Individuals in the supplier organisation should be aware of the scope, responsibility and authority of their functions and their impact on product or service quality.

Adequate authority should be delegated to individuals to allow them to carry out their designated responsibilities. They should have clear understanding of their defined authority and freedom, and designated channels to take action. Everyone in the organisation should be made aware of, the quality objectives, and should feel responsibility for achieving them and for fulfilling the requirements for the quality of its products. It is usual to designate one or more individuals to monitor and to report the quality achieved. It is important that those so designated have access to the highest levels of management in the organisation.

Responsibilities for key elements of the quality system may be defined in a combination of organisation charts and written job descriptions. These key elements include (but are not limited to):

- the control and maintenance of the quality system, aimed at the identification and prevention of quality deficiencies against the specified requirements for the product, process and quality system;

- the control of a corrective action system that prevents the recurrence of the quality deficiencies, by ensuring that changes to the quality system intended to prevent manufacture of nonconforming product are effective;

- organising formal and systematic management reviews of the quality system, to ensure that it remains appropriate to the quality objectives;

- the expert assessment of any procedures for environmental control, and the validation protocols for all processes where environmental control is of significance;

- managerial control of any special processes, and ensuring these operate within validated parameters.

See also 5.2.1, 5.2.2 and 5.2.3 of ISO 9004-1.

4.1.2.2 Resources

Supplier management should recognise that adequate resources and personnel can involve the following:

- people doing the management, performance of work and verification activities;

- awareness of standards and the working arrangements which exist;

- training (see 4.18);

- sufficient time to do the work;

- production schedules which allow time for activities such as inspection, test and verification;

- equipment;

- documented procedures;

- means to access quality records;

Management may consider obtaining specialist professional advice through a sub-contract to another organisation, while employing their own staff to implement agreed procedures in a routine manner. In such cases records of the qualifications of the sub-contracted personnel should be readily available.

See also 5.2.4 and 18.3 of ISO 9004-1.

4.1.2.3 Management representative

The management representative may have other functions. Where this is the case the responsibilities and authorities for both the quality system and the other functions should be clearly defined. Potential conflicts of interest should be examined to ensure that the effectiveness of the quality system is not degraded. The organisational structure should show how the position of the management representative is linked with line management in order that the duties of the management representative can be effectively discharged.To ensure that the management representative's duties remain clearly defined, he/she alone should be authorised to delegate his/her defined authority.

4.1.3 Management review

Management can fulfil its duty to monitor the continuing suitability and effectiveness of the quality system by conducting periodic, systematic reviews.

Such management reviews are additional to, and use the findings of, internal quality audits (see 4.17) conducted to ensure continued adherence to the system. Both management reviews and quality audits should be performed regularly, and not only be conducted as a reaction after quality problems have been identified.
The quality system review process and the reasons behind it should be known and understood by the organisation. Reviews may include the following:

- the organisational structure, including the adequacy of staffing and resources;

- the structure and degree of implementation of the quality system;

- the achieved quality of the end product or service in relation to the requirements for quality;

- information based on purchaser feedback, internal feedback (such as results of internal audits), process performance, and product (including services) performance.

The management should review periodically the appropriateness of the review frequency. The frequency depends on individual circumstances. (Some organisations have found that annual management reviews are appropriate, but this interval is not mandatory).

Activities and results may be evaluated on a systemic and/or random basis. Chronic problem areas should receive special attention. Results should be documented and analysed for trends that may indicate systematic problems.

Required changes to the quality system determined during a management review should be implemented in a timely manner. The effectiveness of any changes should be evaluated.

See also 5.4 and 5.5 of ISO 9004-1.

4.2 Quality system

4.2.1 General

The implementation of a quality system by the supplier is most effective when those in the organisation understand its intention and how it functions, in particular in the area of their responsibility and its interface with other parts of the system.

The quality manual is an essential aid to this understanding by those both inside and outside the supplier's organisation. The quality manual could be one document supported by several tiers of documents, each tier becoming progressively more detailed. For example, there may be an overall system manual and one or more specific procedural manuals. Together these documents define the quality system.

Note: For general guidance on the content of a quality manual, it is recommended to refer to ISO 10013.

One of the tiers of documents supporting the quality manual is a " Device Master File" or " Device Master Record" (DMR) for each product type (see 4.4.5). This contains, or gives reference to the location of, documentation relevant to the design, manufacture, installation and servicing of that product. Examples of such documentation may include:

- specifications for raw materials, labels, packaging materials, intermediate and finished products;

- drawings, software design specifications and source code;

- work instructions (including equipment operation), production methods, environmental specifications;

- sterilization process details (if applicable);

- inspection procedures and acceptance criteria;

- installation and servicing procedures (if applicable).

Such files may also contain quality records (see 4.16) such as:

- design verification records;

- process validation records.

All this documentation forms part of the quality system and should be subject to document control procedures (see 4.5).

4.2.2 Quality system procedures

Documented procedures should exist which show how each element of the quality system requirements is met. These procedures should reflect the supplier's quality policy and organisation and the nature of the product(s) or service(s) being supplied.

The procedures may refer to work instructions that define how an activity is carried out in relation to a specific product, or product type, or service.

4.2.3 Quality planning

Quality plans may be used to define how the quality system requirements will be met for a specific class of products. Most of them will have a sequence of activities in relation to a time frame. Here again the plans can be in several tiers, becoming progressively more detailed. An example could include a detailed sequence of inspections, relating to a product (including service), along with type of inspection equipment and quality record requirements.

Note: For general guidance on quality plans it is recommended to refer to ISO 9004-5

See also 4.4, 5.1, 5.2.5, 5.3.2 and 5.3.3 of ISO 9004-1.

4.3 Contract review

4.3.1 General

4.3.2 Review

The importance of a thorough understanding of the purchaser's needs during the tendering stage at the formulation of the contract and in all subsequent stages, cannot be overstated. Often dialogue will be necessary to achieve this understanding, that should clearly establish the purchaser's requirements as to the product, delivery and other critical factors.

Medical devices may be supplied to customers via telephoned or written purchase orders, or on the receipt of a standing order. Such orders are often based on information supplied to the customer in the form of a sales catalogue. In some situations a documented contract may be agreed between the parties concerned. In all these circumstances a legally binding contract may be deemed to exist and the contract review process should be applied.

Contracts established to permit supply of product by Electronic Data Interchange need especially careful review in order to ensure that the subsequent automatic processes can be operated safely.

4.3.3 Amendment to contract

Amendments to contracts may be introduced by the customer (eg. change of requirements) or by the supplier (eg. inability to meet specification or dates). Changes introduced by the customer should be subjected to the same review procedure as new contracts.

A documented system should exist for ensuring that changes are communicated to all affected parts of the supplier's organisation. Changes introduced by the supplier should be agreed by the customer and this agreement should be documented.

4.3.4 Records

In most cases it should be sufficient for records to be kept to show that a review has taken place. In some cases, particularly where a contract has been amended, it may be advisable to keep more detailed records.

4.4 Design control

4.4.1 General

The essential quality aspects and the regulatory requirements, such as safety, performance, and dependability of a product (whether hardware, software, services, or processed materials) are established during the design and development phase. Deficient design can be a major cause of quality problems. ISO 9001 specifies design control requirements for the design process.

In considering design control, it is important to note that the design function may apply to various facets of the operation in differing styles and time scales. Such facets are related to products, including services and software, as well as to process design associated with product design. The supplier should consider all phases of the design associated with product design. The supplier should consider all phases of the design function process for which controlled procedures are necessary.

The nature of product evaluations, design reviews, process validations, etc, should be proportional to the nature of the risks of the device. Use of techniques such as fault tree analysis and failure mode and effects analysis can be helpful in determining the nature of possible design flaws and the risks that they entail.

See also 8.1 and 19 of ISO 9004-1.

4.4.2 Design and development planning

The design process may become a lengthy and costly process if the design activity is not properly defined and planned.

The supplier's procedures for design and development planning should include such elements as:

- sequential and parallel work schedules with the timescales;

- design verification activities;

- plans for evaluating the safety, performance, and dependability incorporated in the product design;

- plans for methods of product measurement, test, and acceptance criteria;

- assignment of responsibilities.

The design plan typically includes the specific quality practices, assessment methodology, record-keeping, documentation requirements, resources, etc and sequence of activities relevant to a particular design or design category. The plan should reference applicable codes, standards, regulations and specifications. However, the plan should only be as comprehensive as needed to meet the quality objectives.

If any clinical evaluation is necessary, the supplier should consider whether any special documentation is required to comply with regulatory procedures.

The supplier should clearly assign responsibilities for specific design leadership and other design work functions to designated personnel. The personnel in these functions should be qualified and

have access to information and the resources to complete the work.

Design activities should be specified at the level of detail necessary for carrying out the design process and in a manner which permits verification that the design meets the requirements.

See also 8.2.1, 8.2.2 and 8.2.3 of ISO 9004-1.

4.4.3 Organisational and technical interfaces

When input to the design is from a variety of sources, their inter-relationships and interfaces (as well as the pertinent responsibilities and authorities) should be defined, documented, coordinated and controlled.

Many organisational functions contribute to the design process. These may include:

- research and development;
- marketing;
- purchasing;
- quality assurance and quality management;
- engineering;
- regulatory affairs;
- materials technology;
- production/manufacturing;
- service groups;
- facilities management;
- warehousing/transportation/logistics;
- communications facilities;
- information systems.

To function effectively the suppliers' design work groups, both internal and external, should establish:

- what information should be received and transmitted;
- identification of sending and receiving groups;
- the purpose of the information transmittal;
- identification of transmittal mechanisms;
- document transmittal records to be maintained.

4.4.4 Design input

Design inputs are typically in the form of:

- product description specifications, and/or
- product description with specifications relating to configuration, composition, incorporated elements and other design features.

All pertinent design inputs (such as performance, functional, descriptive, environmental, safety, quality assurance and regulatory requirements), should be defined, reviewed and recorded by the supplier in a design description document(s).

This design description document should quantify all requirements wherever practicable. It lays the foundation and provides a unified approach to the design. It also records the resolutions of any incomplete, ambiguous or conflicting requirements which have been uncovered.

The design description document should identify those design aspects, materials, and processes which may require development and analysis, including prototype testing to verify their adequacy. The design description document should be prepared in a way that facilitates periodic updates. It should also indicate "when" and "what criteria" will cause the document to be updated, and who is responsible for the update. A design description document prepared in this way serves as the definitive up-to-date reference document as the design progresses to completion.

The specified requirements for medical devices placed on the market are normally set by the supplier, usually based on his perception of clinical need and the potential market. Design input data may also include advice from an appropriately qualified practitioner. For example, consideration may need to be given to anatomical and physiological implications of the intended use of the product. In developing the specified requirements, the supplier should consider other likely uses of the device and the needs for labels and customer training.

The design transfer process (see 4.4.5) will flow more smoothly if, during design input, consideration is given to production (parts and materials availability, equipment needs, training, etc) and assessment requirements (conformance assessment procedures, methods and equipment).

See also 7, 7.1, 7.2, 8.2.4 and 8.2.5 of ISO 9004-1.

4.4.5 Design output

Throughout the design process, the requirements contained in the design description are translated by the supplier into outputs, such as the following:

- drawings;
- specifications (including process and material specifications);
- work instructions;
- software;
- quality assurance procedures;
- installation and servicing procedures;
- packaging and labelling specifications, including copies of approved labels, methods and processes used.

Outputs of the detailed design are the final technical documents used for purchasing, production, installation, inspection and testing, and servicing.

This information, or reference to the location of this information, constitutes the Device Master Record (DMR) (see 4.2).

As part of, or in addition to, the DMR documents, it is good practice to maintain a file to demonstrate that each design was developed and verified in accordance with the approved design plan. Such a file includes or refers to the location of design documentation such as design input requirements, design verification results, design review results, etc.

The DMR should normally be held (or be reasonably accessible) at each site where the product is manufactured. The design file (if separate) need be held only at the design site.

Design Transfer

The transfer of a design to production typically involves review and approval of specifications and procedures and, where applicable, the proving of the adequacy of the specification, methods and procedures through process validation including the testing of finished product under actual or simulated use conditions.

It may not be possible to determine the adequacy of full-scale manufacturing on the basis of successfully building prototypes or models in a laboratory and testing these prototypes or models. The engineering feasibility and production feasibility may be different because the equipment, tools, personnel, operating procedures, supervision and motivation may be different when a company scales up for routine production. One way to ensure that distributed devices have the quality attributes established during the design phase, and that these are not adversely affected by the production process, is to manufacture finished devices using the approved specifications, the same materials and components, the same production and assessment equipment, and the same methods and procedures that will be used for routine production. Where appropriate, this may be accomplished by manufacturing " pilot runs" or " first production runs".

These devices, or samples from these runs, are then qualified through testing under actual or simulated use conditions, and in the environment (or simulated environment) in which the device is expected to be used. The extent of the testing conducted should be governed by the risk the device will present to the user should it fail and the level of scientific knowledge.

4.4.6 Design review

Design reviews typically are the coordinating design control measure. Design review and/or type testing by an authorised external organisation may be a regulatory requirement for certain types of product.

The competence of the participants in the design reviews should be adequate to permit them to examine designs and their implications. Design reviews for the purpose of design verification can consider questions such as the following:

a. Do designs satisfy all specified requirements for the product (including service)?

b. Are product design and processing capabilities compatible?

c. Has a risk analysis been carried out to ensure that safety considerations are covered?

d. Do designs meet functional and operational requirements, that is, performance and dependability objectives?

e. Have appropriate materials and/or facilities been selected?

f. Is there adequate compatibility of materials and components and/or service elements?

g. Is the design satisfactory for all anticipated environmental and load conditions?

h. Are components or service elements standardised and do they provide for interchangeability, maintainability and replacement?

i. Are plans for implementing the design, for example, purchasing, production, installation, inspection and testing, technically feasible?

j. Can the tolerance requirements consistently be met?

k. Where computer software forms part of the product, or has been used in design computations, modelling, or analyses, has the software (and its configuration control) been

appropriately validated, authorised, and verified?

l. Have the inputs to such software, and the outputs, been appropriately verified and documented?

m. What are the assumptions made during the design process and what is their validity?

Records of design review meetings should be retained. The records should identify those present at the meeting and the decisions reached.

See also 8.4 and 8.6 of ISO 9004-1.

4.4.7 Design verification

ISO 9001 describes design control measures (eg. alternative calculations, tests and demonstrations, comparison with a proven design) which can be used in conjunction with design reviews to verify the design. Design verification should ideally involve personnel other than those responsible for the design work under review.

Once the design is translated into physical form, its safety, performance and reliability should be verified by testing under simulated use conditions. Such verification may include in-vitro and in-vivo testing.

When alternative calculations or comparison with a proven design are employed as forms of design verification the appropriateness of the alternative calculation method, and/or the proven design should be reviewed in relation to this new application.

See also 8.4, 8.5, 8.6, 8.7 and 8.9 of ISO 9004-1.

4.4.8 Design validation

Design validation goes beyond the purely technical issues of verifying that the design output meets the design input, and is intended to ensure that the product meets user requirements. This may involve consideration of who the user really is, the operating instructions, and any restriction on the use of the product.

Clinical evaluation may be involved in the validation of the design of medical devices. The conduct of clinical investigations should conform to applicable regulations/standards.

See also 8.5 of ISO 9004-1.

4.4.9 Design changes

The design of a product may be changed or modified for a number of reasons, for example:

- omissions or errors (eg, due to calculation, material selection, etc.) during the design phase have been identified afterwards;

- manufacturing and/or installation difficulties are discovered after the design phase;

- the purchaser or sub-contractor requests changes;

- the function or performance of a product or service is to be improved;

- safety, regulatory, or other requirements have been changed;

- design verification necessitates change (cf, Clause 4.4.7);

- corrective action necessitates change (cf, Clause 4.14).

Changes during the design phase may require change to the d esign input (4.4.4). The design input should be regarded as a controlled document and any such changes should be made in accordance with the document change procedures (4.5.2).

All design changes should be reviewed to determine whether they influence previously approved design verification results. Design changes in one component of a product should be evaluated for their influence on the whole. Improving one characteristic may have unforeseen adverse influence on another.

When significant design changes are made, the verification procedures (4.4.7) should also be reviewed and modified as appropriate.

Procedures should be established to communicate the new d esign output (4.4.5) to all concerned, to record any design changes, and to ensure, as well as document, that only authorised design changes have been made.

When the design of a medical device which has already been placed on the market is changed, the supplier should consider whether the regulatory authorities should be notified.

See also 8.8 of ISO 9004-1.

4.5 Document and data control

4.5.1 General

Documents and data containing information and/or instructions can be recorded, transmitted or received using a variety of media, such as hard copy or electronic media.

4.5.2 Document and data approval and issue

The supplier's system should provide a clear and precise control of procedures and responsibilities for approval, issue, distribution, and administration of documentation, including the removal, and possibly preservation, of obsolete documents. This can be accomplished, for example, by maintaining a master list of documents identifying level of approval, distribution (location of copies), and revision status.

Document control should include those documents and/or computer records pertinent to design, purchasing, work execution, quality standards, inspection of materials and the quality system documents. The supplier's internal written procedures should describe:

- how the documentation for these functions should be controlled;
- who is responsible for the control;
- what is to be controlled;
- where and when the control is to take place.

4.5.3 Document and data changes

Recognising that supplier documentation may be subject to revision and change, controls should exist for the preparation, handling, approval, issue and recording of changes.

These document controls should apply not only to internal documentation but also to documents, such as regulations and standards, which are generated and updated externally but which may form important parts of the design and manufacturing process. The supplier should establish a continuing mechanism for controlling changes in documentation. The mechanism should:

- provide for control irrespective of documentation media;
- follow documented procedures;
- ensure accurate updating of documents;
- provide for using only authorised documents when implementing changes;
- preclude confusion, especially where there is a multiplicity of sources authorising changes and releasing documents.

Changes that may affect quality should be verified or validated (as appropriate) before implementation.

Consideration should be given to the effect which the proposed changes may have on other parts of the procedure, system, and product (including service). Actions may be needed before a change is implemented to assess the effect of the change on other parts of the organisation, and notify them, as appropriate.

Planned circulation of a change proposal to personnel in the affected functions can assist in avoiding disruption. The timing of the implementation of the change may be an important factor, particularly when several changes of documentation are to be coordinated.

Records of an approved change should include a description of the change, the identity of the

affected documents, a dated signature, and when the change becomes effective.

The master copy of withdrawn documents should be clearly marked and retained by storage in a secure location. Other copies of withdrawn documents should be disposed of. The object of retaining a single copy of obsolete or superseded documents is to provide a full picture of the product at various stages of its life, from first design considerations through development to present status. It may be possible to achieve this objective by maintaining detailed records of changes as they are made, rather than retaining copies of each issue of every document.

See also 17 of ISO 9004-1.

4.6 Purchasing

4.6.1 General

A supplier may purchase, from a number of sources, products and services which may include:

- raw materials;

- components or sub-assemblies manufactured by others using equipment owned by, and/or materials provided by, the supplier;

- components or sub-assemblies available as standard items from other sources;

- components or sub-assemblies manufactured by others to the supplier's specifications;

- completed product bearing the mark and/or name of the supplier; this may be ready for sale or require some further processing such as packaging and/or sterilization;

- services, eg sterilization, calibration, testing, pest control, waste disposal, cleaning, environmental monitoring, laundry, transport, installation.

The term ' sub-contractor' is taken to include all providers of materials, components, sub-assemblies, finished product or services.

A distinction may be made between purchase of materials or services to the supplier's specification and the purchase of standard commercially available materials. This can be useful in deciding on the type and extent of control to be applied to purchased materials or services.

To ensure that purchased, sub-contracted products (including services) conform to specified purchaser requirements as well as regulatory requirements, purchasing should be planned and carried out by the supplier under adequate control. This should include the following:

- evaluation and selection of sub-contractors (see 4.6.2);

- clear and unambiguous specification of the purchaser requirements (see 4.6.3);

- the performance of suitable verification (see 4.6.4);

- inspection procedures (see 4.10.1).

The supplier should establish an effective working relationship and feedback system with the sub-contractor.

See also 9 of ISO 9004-1.

4.6.2 Evaluation of sub-contractors

The supplier may employ several ways of choosing satisfactory sub-contractors, given that technical capabilities are satisfactory for the product to be delivered, for example:

- a review of previous performance in supplying similar products, processes or services;

- a satisfactory evaluation to an appropriate quality system standard by a body considered to be competent for the purpose;

- an evaluation of the sub-contractor by the supplier to an appropriate quality system standard.

The supplier's quality records concerning the evaluation should be sufficiently comprehensive to demonstrate the ability of sub-contractors to meet contract requirements and should allow for selection on the basis of quality capability.

Factors such as product compliance with specified requirements, the total cost for the supplier, delivery arrangements, and the sub-contractor's own quality systems may be pertinent in this context. The performance of sub-contractors should be reviewed at intervals consistent with the complexity and technical requirements of the product and demonstrated sub-contractor performance.

See also 9.3 of ISO 9004-1.

4.6.3 Purchasing data

Clarity in the specification documents and the sub-contractor's agreement that the product or service can be supplied in accordance with the specification, are essential ingredients of success in sub-contracting. The sub-contract should also include an agreement between both parties on the methods of quality assurance that will be used to decide the acceptability of product or service.

The supplier's purchasing data should define the specified technical product requirements to the sub-contractor to ensure the quality of the purchased product, process or service. This may be done, in part, by reference to other applicable technical information such as national or international standards, test methods, etc. Well-defined purchase orders can provide documented evidence. Another option is for essential information to be clearly and precisely stated in the sub-contract. Responsibilities for reviewing and approving the purchasing data should be clearly assigned to appropriate personnel. Arrangements should be made to identify the revision status of documents referenced in the purchasing data.

Where justified by the use of the device, the purchasing agreement should include a requirement for the sub-contractor to give advance notice to the supplier of any changes (eg of materials) that could affect the quality of the product or service supplied.

See also 9.2 and 9.4 of ISO 9004-1.

4.6.4 Verification of purchased product

If the supplier's procedures under 4.6.1-4.6.3 are described and documented in sufficient detail, they will provide satisfactory evidence that purchased product meets specified requirements.

If not, the supplier may find it difficult to satisfy the enquiries of customers or certification bodies. In such cases, the supplier may have to arrange for the customer/certification body to verify directly the sub-contractor's product and/or processes.

4.7 Control of customer-supplied product

"Customer-supplied product" is product owned by the customer and furnished to the supplier. The supplier, upon delivery, accepts responsibilities for prevention from damage, and for identification, maintenance, storage, handling and use while that product is in the supplier's possession.

For parts or medical devices provided by the customer to the supplier, the responsibility for their conformity to an agreed specification lies with the customer. However, the supplier should not knowingly incorporate nonconforming parts into any medical devices supplied to the customer.

4.8 Product identification and traceability

The supplier can achieve product identification by marking or tagging the product or its container. For

example, on visually identical parts where the functional characteristics are different, different colours can be used. For bulk products or product from continuous processes, the identification may be limited to identification of batches or well-defined lots.

Service identification can be achieved by documentation that accompanies the service.
Product (including service) traceability involves the ability to trace the history, application, or location of an item or activity by means of recorded identification. Traceability can entail high cost and the extent of this requirement should be carefully considered. The traceability requirement of the destination country should always be considered when establishing traceability procedures.

The supplier can achieve traceability by each individual product having an identifier (eg serial number, date code, batch code, lot number) unique to the source of operation.

Separate identifiers could be required for changes in operative personnel, changes in raw materials, changes in tooling, new or different machine set-ups, changes in process methods, etc. Traceability identifiers should appear on applicable inspection and stock records.For example, adequate traceability can avoid the unnecessary explant of implantable medical devices through precise identification of those implants which incorporate a subsequently identified faulty component, or for which some process control has subsequently been shown to be inadequate. This implies continuing the traceability up to the point of implantation, although this may not always be within the capability of the supplier.

Traceability records should be maintained throughout the lifetime of the product.

See also 11.2 of ISO 9004-1.

4.9 Process control

The supplier's planning for the production and, where applicable, installation processes should consider each of the controlled conditions described in ISO 9001. Control within the process to prevent nonconformities from occurring is preferable to inspection of finished product or service alone. The characteristics which are most critical to the product/service quality should be identified and should be under the closest process control.

Both written and electronic media documentation methods should be recognised for documented procedures.

Process-control activities may include procedures for accepting materials or items into the process and determining their characteristics while in the process. The amount of testing and inspecting needed for process control may bear a relationship to the influence of nonconformities on the downstream process. The adequacy of measurement processes should be considered in assessing the adequacy of production process control.

Where suitable, process control should include statistical process-control methods, supplemented by procedures to maintain the suitability of software, of in-process materials, and of activities needed for appropriate storage, handling, and segregation.

Where the achievement of desired levels of process control is dependent upon consistent and stable operation of process equipment and essential materials, the supplier should include within the scope of the quality system the proper maintenance of such process equipment and essential materials.

Before and during the introduction of a new or significantly changed product (see also 4.4 of this guidance), the manufacturing process, including any new manufacturing and test methods, should be fully evaluated. The key variables and acceptance limits should be identified and validated for processes, test methods and sampling plans. Similar procedures should be followed where any significant change in processing occurs. The results of validation exercises should be documented.

Processes should be re-examined at appropriate intervals to ensure that they are operating within the validated acceptance limits.

Work in Progress

Work-in-progress should be identified and/or segregated to avoid product mix-up and to ensure traceability where necessary (see 4.8 of this guidance). For small parts, for bulk manufacture, and where the parts cannot be marked, the bulk containers and/or process equipment may be identified to indicate the product and/or batch. This identification need not be the code used on the finished product, but it should be easily related to this code. Any previously used labels should be removed or obliterated.

Ancillary materials should be adequately identified and labelled. Containers for temporary storage and handling should be suitably constructed and cleaned as necessary.

Equipment

Where automated production or quality control systems are used, any software and/or hardware should be validated. Software and changes to software may be controlled in the same manner as documents, i.e. program authorised on issue, master copy of the original program retained, control and validation of changes to programs with revision levels, and retention of superseded copies (see also section 4.5 of this guidance). ISO 9000-3 may be used as a reference in the control of software.

Maintenance of equipment

Documented procedures should be available for the maintenance and checking of all equipment used in production and for environmental control. The determination of the necessary adjustments and maintenance intervals should be established during the commissioning and validation of new equipment.

Premises

The design, construction and maintenance of premises can influence product quality. Buildings in which manufacture, assembly, packaging, storage, inspection and test, and labelling are carried out should be of suitable design and contain sufficient space to facilitate cleaning, maintenance and other necessary operations.

The following are examples of features to be considered in the design and construction of premises: lighting, temperature, humidity, ventilation, air pressure, filtration, airborne particulate contamination, microbial contamination, and possibility of electrostatic discharge. Special handling procedures may be required to protect circuit components from damage due to electrostatic discharges.

Features which can affect the quality of product, may include: cleanliness, environmental conditions, segregation of materials, access for personnel, storage facilities, waste disposal arrangements, and provision for eating, drinking and smoking areas. Some of the provisions that should be considered where they may affect product quality are:

- flow of material through manufacturing;
- access for personnel;
- cloakroom and toilet facilities, segregated from production areas;
- maintenance, repair, building activities; the desirability of documenting maintenance activities;
- pest control; the avoidance of product contamination by pest control materials
- gas, electricity, water, etc;
- special manufacturing operations;
- the segregation of "dirty", or dust-generating, activities from "clean" processes or areas;
- disposal of waste material;
- special storage areas and conditions;
- special testing and laboratory facilities.

Cleaning of premises and equipment

Documented cleaning procedures for all general areas and equipment may include:

- cleaning equipment and materials to be used;
- methods to be used;
- methods of protection of products from contamination during cleaning;
- frequency of cleaning;
- designated personnel;
- records to be kept;
- instructions for periodic major cleaning;
- storage of cleaning equipment in a clean, dry and tidy manner.

When cleaning operations are carried out by a sub-contractor, there should be a written contract

specifying the limits of responsibility of both parties. This contract should include details of the documented cleaning procedure and specify the training to be given to cleaning staff (see also 4.18 of this guidance).

Installation

If a medical device has to be assembled or installed at the user's site, instructions should be provided by the supplier to guide correct assembly, installation and/or calibration, which is the final stage of manufacture. Special attention should be paid to correct installation of safety control mechanisms and safety control circuits.

In certain cases, for example when required by regulation, where performance parameters of a medical device have to be controlled, the supplier should provide instructions that allow the installer to confirm correct operation of the device. The results of installation or commissioning tests should be documented.

Special Processes

The supplier should give special consideration to "special processes". These are processes in which the product quality characteristics cannot fully be verified in the finished product.

Examples include circumstances where:

- the characteristics of interest do not exist until further downstream in the process;

- the method of measurement does not exist or is destructive to the product;

- results within the process cannot be measured in later inspections or tests;

All products are produced by processes, and "special processes" are found in all generic product categories: hardware, software, processed materials, and services. However, "special processes" are particularly common in producing processed materials.

Some examples where critical product quality characteristics fall within one or more of the three process circumstances above include:

- strength, ductility, fatigue life, corrosion resistance of a metal part following welding, soldering, heat treatment or plating;

- dyeability, shrinkage, tensile properties of a polymer;

- correct implementation of a software product, or cleanliness/sterility of a medical device.

Such products are typically the final result of a series of operations and require close adherence to specified in-process procedures and sequences. For a processed material or hardware product these can involve starting materials, temperature profiles, physical deformations, mixing and environmental conditions. For a software or service product these can involve source data and documents, intellectual and clerical correctness.

Comprehensive measurement assurance and calibration of equipment used to produce or measure the product may be required for such "special processes". The use of statistical process control is often most advantageous.

Special skills, capabilities and training of personnel may be needed and should be demonstrated.

Process knowledge can be considered as a basis to distinguish finished-product characteristics from measurable in-process characteristics. Such processes should be validated in advance to ensure that the process will meet the specified requirements.

See also 10, 11 and 16.3 of ISO 9004-1.

4.10 Inspection and testing

4.10.1 General

See also 8.3 and 10.1.4 of ISO 9004-1.

4.10.2 Receiving inspection and testing

4.10.2.1 Receiving inspection is one means for the supplier to verify that sub-contractors have fulfilled their contractual obligations relating to quality and that procured items entering the supplier's facilities fulfil specified requirements for quality.

4.10.2.2 This clause in ISO 9001 does not imply that incoming items have to be inspected and tested by the supplier, if the necessary confidence in the product (including service) can be obtained by other defined procedures.

The supplier's procedures or quality plan should specify the means of verifying that shipments received are in accordance with specifications, are complete, have the proper identity and are undamaged. The procedures should also include provisions for verifying that incoming items, materials or services are accompanied by supporting documentation as, and if, required (eg. certificates of analysis, test results). Appropriate action in the event of nonconformities should be specified. Analysis of past receiving inspection data, in-plant rejection history or customer complaints can influence the supplier's decisions regarding the need to reassess a sub-contractor.

4.10.2.3 The supplier's procedures should define responsibilities and authority of personnel who may allow incoming product(s) to be used without prior demonstration of conformance to specified requirements for quality. The supplier's procedures should also define how such product(s) will be positively identified and controlled in the event that subsequent inspection finds nonconformities.

See also 9.7, 9.8 and 12.1 of ISO 9004-1.

4.10.3 In-process inspection and testing

In-process inspection and testing applies to all forms of products, including services. It allows early recognition of nonconformities and timely disposition of the nonconforming items.

Where appropriate, statistical control techniques should be used to identify trends for both product and process before nonconformities actually occur.

The supplier's procedures or quality plan should ensure the objectivity of the inspection and test results, including situations where in-process inspection is carried out by production personnel.

Early identification of nonconformities, before arriving at the final inspection stage, increases the efficiency of the entire operation by avoiding further processing of nonconforming items.

See also 10.1.2, 10.1.3 and 12.2 of ISO 9004-1.

4.10.4 Final inspection and testing

Final inspection involves the activities (examination, inspection, measurement or test) upon which the final release of product (including service) is based with respect to specified characteristics. The specified requirements forming the basis of final inspection and test should include all designated release characteristics. These should be directly related to the type of medical device involved and its intended use. Final testing may include, where practical, testing under simulated or actual conditions of use of products selected from a lot or batch.

In the case of equipment which is assembled and/or installed at the user's premises, the final inspection and testing can only be carried out after the completion of assembly/installation. In such cases, the final inspection and test may not be carried out by the supplier but the supplier should ensure the availability of all necessary information about the inspection and test procedure and the

results expected.

See also 12.3 of ISO 9004-1.

4.10.5 Inspection and test records

The supplier's inspection and test records should facilitate assessment of products having fulfilled the requirements for quality. Helpful supporting evidence may be available from records of other inspections and tests (eg raw materials, in-process). Regulatory requirements and product liability should also be taken into consideration.

Methods of recording the results of inspections and tests include:

- documentation regarding the product;
- electronic records, and
- separate test reports.

As applicable, records may:

- identify the inspection/test procedure(s) and revision level used (see also 4.5);
- identify the test equipment used;
- be signed and dated by the person responsible for the inspection or test;
- clearly identify the number of items examined and the number accepted;
- record the disposition of any items failing inspection or test, and the reasons for failure.

Final product release should be authorised by the signature of a designated person.

See also 17.3 of ISO 9004-1.

4.11 Control of inspection, measuring and test equipment

4.11.1 General

4.11.2 Control procedure

The requirements of this clause in ISO 9001 spell out in considerable detail what is to be implemented. Although the requirements pertain explicitly to inspection, measuring and test equipment, it is helpful to approach the subject from the perspective that measuring is itself a process involving raw materials, equipment and procedures. The requirements of ISO 9001 explicitly involve elements of the measurement process; elements whose collective purpose is to choose suitable measurements, suitable measuring equipment, and suitable measurement procedures. These elements are specified to provide confidence in the ability of the supplier's measuring systems to control adequately the production and inspection of the product.

For both product- and process-measurement systems, statistical methods are valuable tools for achieving and demonstrating fulfilment of requirements. In particular, statistical methods are the preferred tools in fulfilling the requirement that "Inspection, measuring and test equipment shall be used in a manner which ensures that the measurement uncertainty is known and is consistent with the required measurement capability".

The requirements of this clause also should be applied by the supplier insofar as "demonstrating the conformance of product to the specified requirements" contractually involves measurements subsequent to production and inspection of a product (eg. during subsequent handling, storage,

packaging, delivery or servicing) as may be required under other clauses of ISO 9001.

Note: See also ISO 10012-1.

See 13 of ISO 9004-1.

4.12 Inspection and test status

The supplier's quality system and procedures should ensure that required inspections and tests are performed. The system should provide a way of knowing the product (including service) status. Status may be indicated by marking or tagging or signing, either physically or by electronic means. Status should indicate whether a product has
not been inspected, has been inspected and rejected and on hold awaiting decision, or has been inspected and rejected. Separate physical location of these categories of
product units is often the most certain method of assuring both the status and accurate disposition. However, in an automated environment accurate disposition may equally be achieved by other means, such as a computer data base.

See also 11.7 of ISO 9004-1.

4.13 Control of nonconforming product

4.13.1 General

When any intermediate or final product (including service) is found (eg by test or inspection) not to conform to the technical specifications, inadvertent use or installation should be prevented. This is applicable to nonconforming product occurring in the supplier's own production as well as nonconforming product received by the supplier. Procedures are established and maintained by the supplier for the following purposes:

- to determine and document which product units are involved in the nonconformity, for example, what production time interval, or production machines, or product lots are involved;

- to mark the nonconforming product units to make sure that they can be distinguished from conforming product units (see 4.12);

- to evaluate and document the nature of the nonconformity;

- to consider the alternatives for disposition of the nonconforming product units, to decide what disposition should be made, and to record this disposition;

- to control (eg by physical segregation) the movements, storage and subsequent processing of the nonconforming product consistent with the disposition decision;

- to notify other functions that may be affected by the nonconformity, including, where appropriate, the purchaser.

An important element in addressing nonconformities is to give to all appropriate personnel the freedom to identify nonconforming items, activities and processes and encouragement to suggest improvements.

Any product returned to the supplier should be treated as nonconforming product until it has satisfied a documented acceptance procedure.

Before returned medical devices which may have been contaminated with biological material are handled, they should be decontaminated according to appropriate, approved procedures.

See also 11.8 and 14 of ISO 9004-1.

4.13.2 Review and disposition of nonconforming product

It is suggested that nonconformity disposition decisions made by the supplier take into consideration the six purposes listed under 4.13.1, in relationship to the risk of failure to meet the purchaser's requirements. Actions a, b, c, d, in ISO 9001 all carry degrees of risk.

Concessions or changes in specification should be processed in accordance with documented procedures. If a product is allowed to be released under concession or is reworked, this should be recorded in the Device History Record (see 4.16). Any concession should be adequately justified, and the justification should be recorded.

4.14 Corrective and preventive action

4.14.1 General

It is important that the causes of detected (or potential) nonconformities be promptly identified in order that a programme to prevent recurrence (or occurrence), may be developed.

These causes may include:

- failures, malfunctions or nonconformities in incoming materials, processes, tools, equipment or facilities in which products are processed, stored or handled, including the equipment and systems therein;
- inadequate or nonexistent procedures and documentation;
- noncompliance with procedures;
- inadequate process control;
- poor scheduling;
- lack of training;
- inadequate working conditions;
- inadequate resources (human or material);
- inherent process variability;

The conditions resulting from these causes may be revealed by analysis of both internal and external observations.

Internal observations may include:

- inspection and test records;
- nonconformity records;
- observations during process monitoring;
- audit observations;
- observations and reports by the supplier's personnel;
- sub-contract problems;
- management review results.

External observations ("feedback") may include:

- reports from the marketing function;

- reports from authorised representatives;
- service records;
- customer complaints or reports;
- returned product;
- solicited information on new or modified products;
- reports from regulatory authorities;
- published literature.

Regulations may place requirements on suppliers to monitor the use of their products and inform regulatory authorities of certain defined experience in use.

4.14.2 Corrective action

The supplier's procedures should clearly establish responsibility for taking corrective action, how this action will be carried out, and verification of the effectiveness of the corrective action. An important element in the programme is the dissemination of quality problem information to those directly responsible for ensuring quality.

The procedures for dealing with nonconformities discovered in product which has already been shipped as satisfactory can include, among others:

- investigations to establish whether the nonconformity is an isolated or a chronic problem;
- if necessary, taking such actions as:
- withholding products available for sale;
- withdrawing products from circulation;
- giving advice to customers: this may take the form of checks to be carried out before use, providing additional guidance on the use of the product or for the replacement of certain products;
- in extreme cases, the recall of products.

Complaints

Any complaint received by the supplier on a product which either i) fails to conform with its specification, or ii) conforms with its specification but nevertheless causes a problem in use should fall under the complaints system. For instance, a complaint with a conforming product may be caused by a fault in the design.

The documented complaints system should cover the following:

establishing responsibility for operating the system;

evaluation of the complaint;

records and statistical summaries, enabling the major causes of complaints to be determined;

- any corrective action;
- segregation and disposition, or reprocessing, of customer returns and faulty stock (special attention may need to be given to decontamination);
- filing of customer correspondence and other relevant records; the retention time for

these should be defined.

The documentation of complaint investigations should contain enough information to show that the complaint was properly reviewed. For example: a determination of whether there was an actual product failure to perform per specifications; whether the product was being used to treat or diagnose a patient; whether a death, injury or serious illness was involved; the relationship, if any, to the reported incident or adverse event. An investigation record would typically include:

1. the name of the product;

2. the date the complaint was received;

3. any control number used;

4. the name and address of the complainant;

5. the nature of the complaint;

6. The results of the investigation, including:

   - the corrective action taken
   - the justification, if no action is taken
   - the dates of the investigation
   - the name of the investigator
   - the reply (if any) to the complainant.

Where the technical staff who are responsible for an investigation are located at a site other than the place of manufacture of the medical device, the supplier should copy the records of the complaint and the investigation to the manufacturing plant, so that the staff at that plant can be fully informed of the events.

Advisory notices and product recall

The nature and seriousness of the fault, the intended use of the product and the consequential potential for patient injury or harm, will determine whether it will be necessary to issue an advisory notice, to institute a recall and/or to report to local or national authorities. These factors will also determine the speed and extent of the action.

A person, with nominated deputies to cover for periods of absence, should be designated to coordinate the issue of each advisory notice or recall and the consequent actions.

The procedures for generating, authorising and issuing an advisory notice or recall should specify:

- the management arrangements that enable the procedure to be activated, even in the absence of key personnel;

- the level of management that determines that the procedure should be initiated, and the method of determining the affected products;

- the possible necessity to report to local or national authorities, the points of contact and methods of communication between the supplier and national authorities.

An advisory notice or recall should provide:

- the description of the medical device and model designation;

- the serial numbers or other identification (for instance batch or lot numbers) of the medical devices concerned;

- the reason for the issue of the notice/recall;

- advice of possible hazards and consequent action to be taken.

The progress of a recall should be monitored and amounts of product received should be reconciled.

4.14.3 Preventive action

Documented procedures addressing the actions described in this sub-clause of ISO 9001 should be developed by the supplier. In particular, they should establish responsibility for taking preventive action, how this action is to be implemented and the verification of the effectiveness of the preventive action.

See also 7.3, 15 and 16.5 of ISO 9004-1.

4.15 Handling, storage, packaging, preservation and delivery

4.15.1 General

The supplier's system for handling, storage, packaging and delivery of materials should provide proper planning, control, and documentation. This includes in-process materials and finished product.

See also 16 of ISO 9004-1.

4.15.2 Handling

Careful planning and appropriate operating procedures help to ensure that the handling of incoming product, product in process and completed or released medical devices does not jeopardise quality.

The supplier's method for handling materials should consider providing transportation units (such as pallets, containers, conveyors, vessels, tanks, pipelines and vehicles) so that damage, deterioration, or contamination (due to vibration, shock, abrasion, corrosion, temperature variation, radiation or any other conditions occurring during handling and storage) may be prevented. Maintenance of handling equipment is another factor to be considered.

4.15.3 Storage

The supplier should plan for suitable storage facilities, considering not only physical security but also environmental conditions (eg temperature and humidity). It may be appropriate to check periodically items in storage to detect possible deterioration. The methods for marking and labelling should give legible, durable information in accordance with the specifications. Consideration may need to be given to administrative procedures for expiry dates, and stock rotation and lot segregation.

Orderly storage conditions enable rapid and accurate identification of stock and facilitate cleaning, while minimising risk of damage. Storage management procedures should be reviewed by the person responsible for quality assurance.

Raw materials and products which have been rejected, recalled or returned should be identified and may be placed in quarantine to prevent confusion with other materials. Access to materials in quarantine areas should be restricted to authorised persons. Release and disposition should be carried out according to a defined procedure.

4.15.4 Packaging

The packaging of medical devices is intended to provide appropriate protection against damage,

deterioration or contamination, during storage and transportation up to the point of use. The various forms of storage and the types of transportation that might be encountered therefore should be considered, and the effectiveness of the packaging checked.

Where the packaging of the product has been subcontracted it remains the responsibility of the supplier to ensure that the requirements of 4.15.4 are met.

Labelling

The content of labels may be specified in regulations, general standards or product standards. Where product is to be supplied to countries with different languages, and the language to be used on the labels has been agreed, it is advisable for the label translations to be checked by a person whose native language is the agreed language and who has some technical knowledge of the product. Translation problems can be reduced by the use of internationally-agreed symbols.

Where appropriate a record should be retained of the identity of the person who confirms that the correct label(s) has been fixed to and supplied with the medical devices.

The risk of labelling and packaging errors may be minimised by the introduction of appropriate controls such as:

- segregation of packaging and labelling operations from other manufacturing (or other packaging and labelling) operations;

- avoidance of packaging and labelling product of similar appearance in close proximity;

- line identification;

- application of line clearance procedures;

- the destruction of unused batch coded materials on completion of packaging and labelling;

- use of roll feed labels;

- use of known number of labels and reconciliation of usage;

- on-line batch coding;

- use of electronic code encoders/readers and label counters;

- use of labels designed to provide clear product differentiation;

- inspection of label content before use;

- proper storage of labels in areas of restricted access.

4.15.5 Preservation

Shelf-life commences during manufacture and may be influenced by the conditions of storage. The identification of items with a limited shelf life, or which require special protection during storage, is important to ensure that such items are not issued if their shelf life has expired. The supplier should have means of informing the customer or user about any special storage conditions which may apply.

4.15.6 Delivery

The supplier should provide for protection of the quality of product during shipping and other phases of delivery. For some products, including services, delivery time is a critical factor. Consideration should be given to the various types of delivery and variations in environmental conditions that may be encountered.

The traceability requirements of 4.8 may require the maintenance of distribution records.

4.16 Control of quality records

Quality records should contain evidence that the product (including service) meets technical requirements.

The supplier's quality records should provide evidence that the quality system elements of ISO 9001 have been implemented. If the results have not proved satisfactory, quality records should indicate what has been done to correct the situation.

Quality records should be prepared, stored safely, protected from unauthorised access and protected from alteration and maintained by the supplier. They should be readily accessible as and where needed.

Quality records may be stored in any suitable form, for example, hard copy or electronic media. Such copies of quality records should contain all the relevant information in the original quality records. The system for record retention should allow retrieval of quality records without undue delay if required for corrective action (see 4.14).

There may be circumstances in which the purchaser is required to store and maintain selected quality records attesting to the quality of products (including services) for a specified part of the operating lifetime. The supplier should make due allowance for the provision of such documents to the purchaser.

Quality records can be divided into three broad categories:

1. those which relate to the design, and the manufacturing processes, affecting all products of a particular type (pre-production records);

2. those which relate to the manufacture of an individual product or batch of product (manufacturing records);

3. those which demonstrate the effective operation of the overall quality system (system records).

Pre-production records

Examples of records in this category include:

- the contents of the DMR (see 4.2);

- design verification and design review records;

- records of process validation, including sterilization validation (where applicable).

Manufacturing Records

Quality records of category 2 which facilitate traceability and review of the manufacture of a product or batch, derived during the manufacture of that
product/batch should be collated or referenced in a single file. Such files can be referred to as Device History Record, Batch Manufacturing Record, Lot History Record or Lot Record.

If it is not practical to include all the relevant documents in the manufacturing records then they should list the titles of those documents and their location.

Manufacturing records should be prepared from the currently approved versions of the appropriate specifications.

The forms which constitute the manufacturing records are preferably designed and reproduced by an appropriate method to avoid clerical errors. A manufacturing record should be identified by a unique identifier relating to an individual product or manufacturing batch.

During manufacture, relevant information is entered on to the manufacturing record, such as:

- the quantity of the raw materials, components and intermediate products, and their batch number, where appropriate;

- the date of start and completion of different stages of production, including sterilization records where appropriate;

- the quantity of product manufactured;

- the results of all inspections and tests;

- designation of the production line used;

- any deviation from the manufacturing specifications;

- the results of installation/commissioning tests where devices are assembled on site;

- distribution records (where appropriate).

System records

Examples of activities generating records in this category include the following:

- management review;

- contract review;

- complaint handling;

- training;

- internal audits;
- cleaning and maintenance of buildings and equipment;

- environmental monitoring;

- calibration of manufacturing and inspecting equipment.

See also 5.3.4 and 17 of ISO 9004-1.

4.17 Internal quality audits

Internal quality audits as required by ISO 9001 are carried out by the supplier in order to determine whether the various quality system elements of the organisation are effective and suitable for achieving the stated quality objectives. The internal audit plan should include the frequency of periodic audits.

The supplier should select and assign competent auditors for the activity being audited.

Periodic internal audits are performed:

- to determine the adequacy and conformity of the quality system elements with the requirements for their documentation and implementation requirements;

- to determine the effectiveness of the implemented quality system in meeting the specified quality objectives;

- to meet regulatory requirements;

- to provide an opportunity to improve the supplier's quality system;

- to facilitate external quality assurance.

A well-established system of internal auditing is to examine the different sections of the operation individually and in turn so that the entire operation is covered in the course of a reasonable period. Such a system can be operated flexibly to give special, or repeat, attention to any areas of weakness.

In addition to the periodic internal audits, an internal audit may be initiated for any of the following reasons:

- initially to evaluate the quality system;

- to verify that the quality system continues to meet specified requirements, and is being implemented;

- when significant changes have been made in functional areas, for example, revisions of organisations and procedures which affect quality processes;

- when safety, performance or dependability of the products (including services) are in, or are suspected to be in, jeopardy due to nonconformities;

- when it is necessary to verify that required corrective actions have been taken, and have been effective;

- when the quality system is evaluated against a quality system standard.

Target dates for responding to audit observations should be established.

Only records which demonstrate that an effective internal audit system is in operation need to be made available to third party auditors. This may be done by:

- providing documented procedures for the conduct of audits;

- providing audit schedules;

- demonstrating that internal audits have been performed;

- demonstrating that corrective actions have been initiated and completed.

Note: For general guidelines for auditing quality systems it is recommended to refer to ISO 10011-1, ISO 10011-2 and ISO 10011-3, but the guidance in ISO 10011 Parts 1, 2, 3 does not add to, or otherwise change, the requirements of ISO 9001.

See also 5.4 of ISO 9004-1.4.18 Training

The training of personnel in an organisation is essential for the achievement of quality objectives. This includes specific training necessary for performing assigned tasks and general training both to build incentives and to heighten quality awareness. Personnel should be trained in the usage of, and the underlying reasons for, the procedures and documents in the quality management approach of the supplier.

Training should be given as an introduction to new employees and for all personnel engaged in work affecting quality at intervals, and should:

- include the intended use of the products;

- identify quality problems which could arise from the inadequate or improper performance of the specified tasks;

- describe any specific hygiene requirements

- include instruction on conduct to avoid jeopardizing the integrity of special environmental conditions, when applicable;

- include, when appropriate, procedures to be followed on receipt of customer feedback.

To achieve and maintain proficiency a number of steps can periodically be taken by the supplier as follows:

- evaluation of the general education, experience and proficiency of the personnel for the activities to be performed;

- identification of the individual training needs against those required for satisfactory performance;

- planning, organisation and conduct of appropriate training, either in-house or by an outside body;

- recording of training and achievement so that records can be updated and gaps in training can readily be identified and filled.

See also 18 of ISO 9004-1.

4.19 Servicing

Servicing is not an applicable requirement for many medical devices (such as single-use devices), but when the functionality of products depends on regular maintenance and/or repair, the following activities should be considered:

- clarification of servicing responsibilities among supplier, distributors and users;

- planning of service activities and maintenance intervals, whether the servicing is carried out by the supplier or by a separate agent;

- validation of the design and function of special-purpose tools or equipment for handling and servicing products after installation;

- control of measuring and test equipment used in field servicing, testing and calibration, as in the case of such equipment used in manufacture (see 4.11);

- provision and suitability of documentation for servicing the product, including parts lists and circuit diagrams where appropriate;

- provision for adequate back-up, to include technical advice and support, customer personnel training, and spares or parts supply;

- assurance of the quality of spares and replacement components;

- training of servicing personnel;

- provision of competent servicing personnel;

- feedback of information that would be useful for improving product, manufacture or quality system.

Records of servicing activities should be maintained in sufficient detail to identify the reason for the activity and to demonstrate that it was properly carried out.

Some medical devices may need to be cleaned and/or decontaminated prior to servicing. In such cases they should be decontaminated by appropriate, approved procedures.

See also 16.4 of ISO 9004-1.

4.20 Statistical techniques

4.20.1 Identification of need

The use of statistical methods can be beneficial to the supplier in a wide range of circumstances, including data collection, analysis and application. They assist in deciding what data to obtain, and in making the best use of the data, to gain a better understanding of customer requirements and expectations. Statistical methods may be useful in product, service, and process design, in process control, nonconformity avoidance, problem analysis, risk determination, finding root causes, establishing product and process limits, forecasting, verification, and measurement or assessment of quality characteristics.

4.20.2 Procedures

Statistical methods that may be beneficial for these purposes include:

- graphical methods (histograms, sequence charts, scatter plots, Pareto diagrams, cause and effect diagrams, etc) that help to diagnose problems and suggest appropriate computational approaches to further statistical diagnosis;

- statistical control charts for monitoring and controlling production and measurement processes for all types of product (hardware, software, processed materials, and services);

- design of experiments for determining which candidate variables have significant influence on process and product performance, and for quantifying the effects;

- regression analysis, which provides a quantitative model for the behaviour of a process or a product when the conditions of process operation or product design are changed;

- analysis of variance (separating the total observed variability) leading to variance component estimates useful for designing sample structures for control charts and for product characterisation and release; the magnitudes of the variance components are also a basis for prioritizing quality improvement efforts;

- methods of sampling and acceptance;

- sampling of products between production sectors;

- statistical methods for inspection and testing.

The documentation resulting from the application of statistical methods can be an effective means of demonstrating conformance to requirements for quality, and can be used as a form of quality records.

The number of items sampled from any batch should be based upon an established statistical rationale, the past history of the source of supply, and the quantity needed for analysis and retention.

See also 20 of ISO 9004-1.

ANNEX 1

Key to the use of the Guidance Document in conjunction with the Japanese Regulations of Quality Assurance of Medical Devices.

REGULATIONS ARTICLE	GUIDANCE CLAUSE NUMBER
Article 2 - Responsibility of Manufacturer of Medical Devices	4.1.1, 4.1.3
Article 3 - Quality Assurance Organisation	4.1.2
Article 4 - Responsible Technician	4.1.2.3
Article 5 - Personnel Responsible for Design Control, etc	4.4.2
Article 6 - Responsible Quality Assurance Auditor, etc	4.17
Article 7 - Preparation of Product Standard Code, etc	4.2.1
Article 8 - Product Standard Code	4.4.5
Article 9 - Quality Assurance Standard Code	4.2.1
Article 10 - Design Control	4.4
Article 11 - Document Control	4.5
Article 12 - Purchase Control	4.6
Article 13 - Identification Control and Post Manufacturing Records Control	4.8
Article 14 - Manufacturing Process Control	4.9
Article 15 - Testing and Inspection Control	4.10, 4.11, 4.12
Article 16 - Control of Nonconforming Product	4.13
Article 17 - Control of Handling, Storage, Packaging, Labeling and Attached Documents	4.15
Article 18 - Installation	4.9
Article 19 - Pre-delivery Quality Assurance	4.15.6

REGULATIONS ARTICLE			GUIDANCE CLAUSE NUMBER
Article 20	-	Maintenance and Overhaul	4.19
Article 21	-	Dealing with Complaints	4.14
Article 22	-	Product Recall	4.14
Article 23	-	Internal Quality Audits	4.17
Article 24	-	Training	4.18
Article 25	-	Records	4.16
Article 26 more	}	Production involving two or	4.6
Article 27	}	Manufacturing Plants	

ANNEX 2

Key to the use of the Guidance Document in conjunction with the US Good Manufacturing Practice Regulation.

GMP REGULATION PARAGRAPH	GUIDANCE CLAUSE NUMBER
820.5 Quality System	4.2
820.20 Management Responsibility a) Quality Policy b) Organisation c) Management Review	4.1 4.1.1 4.1.2 4.1.3
820.22 Quality audit	4.17
820.25 Personnel a) General b) Training c) Consultants	 4.18 4.6.2
820.30 Design Controls a) General b) Design and development planning c) Design input d) Design verification e) Design review f) Design output g) Design transfer h) Design release i) Design changes j) Design history record	4.4 4.4.1 4.4.2, 4.4.3 4.4.4 4.4.7, 4.4.8 4.4.6 4.4.5 4.4.5 4.4.5 4.4.9 4.4.5
820.40 Document controls a) Document approval and issue b) Document distribution c) Document changes d) Document change records	4.5 4.5.2 4.5.2 4.5.3 4.5.3
820.50 Purchasing Controls a) Assessment of suppliers and contractors b) Purchasing forms	4.6 4.6.2 4.6.3
820.60 Identification and traceability	4.8

GMP REGULATION PARAGRAPH	GUIDANCE CLAUSE NUMBER
820.65 Critical devices, traceability	4.8
820.70 Production and process controls a) General b) Environmental control c) Cleaning and sanitation d) Personnel health and cleanliness e) Contamination control f) Sewage and refuse disposal g) Equipment h) Automated processes	4.9 4.9 4.9 4.9 4.9 4.9 4.9 4.9 4.9
820.75 Special processes	4.9
820.80 Inspection and testing a) General b) Receiving inspection and testing c) In-process inspection and testing d) Final inspection and testing e) Inspection and test records	4.10 4.10.1 4.10.2 4.10.3 4.10.4 4.10.5
820.84 Inspection, measuring and test equipment a) Calibration b) Calibration standards c) Calibration records d) Maintenance e) Facilities	4.11 4.11 4.11 4.11 4.11 4.11
820.86 Inspection and test status	4.12
820.90 Nonconforming components and devices a) Control of nonconforming components and devices b) Nonconformity review and disposition	4.13 4.13.1 4.13.2
820.100 Corrective Action	4.14
820.120 Handling	4.15.2
820.122 Storage	4.15.3, 4.15.5
820.124 Distribution	4.15.6
820.126 Installation	4.9
820.160 Device packaging	4.15.4

GMP REGULATION PARAGRAPH	GUIDANCE CLAUSE NUMBER
820.162 Device labeling	4.15.4
820.180 Records - General requirements a) Confidentiality b) Record retention period	4.16 - -
820.181 Device master record (DMR)	4.2, 4.4.5
820.184 Device history record	4.16
820.198 Complaint files	4.14
820.200 Servicing a) Service records b) Service record evaluation	4.19 4.19 4.14, 4.19
820.250 Statistical techniques	4.20